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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,241	09/25/2003	Mark Korsten	6915-66816	8718

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EXAMINER	
KIM, JENNIFER M	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
12/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,241	KORSTEN ET AL.	
	Examiner	Art Unit	
	JENNIFER M. KIM	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,12-14,18,20-23,25,26 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 9, 12-14, 18, 20-23, 25, 26 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 15, 2008 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites the limitation "acetylcholinesterase inhibitor and the anti-cholinergic agent" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 14 recites the limitation "anti-cholinergic agent… the acetylcholinesterase inhibitor" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 9, 12-14, 18, 20-23, 25, 26 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ponec et al. (1999) in view of Vavilala et al. (1999, both of record and further in view of Casadio (EP 0140434 A2).

Ponec et al. teach that neostigmine is useful for the treatment of acute colonic pseudo-obstruction. (title). Ponec et al. teach that in patients with acute colonic pseudo-obstruction who have not had a response to conservative therapy, treatment with neostigmine rapidly decompresses the colon. (page 137, left-hand column under Conclusions). Ponec et al. teach that side effect of neostigmine of symptomatic bradycardia developed in two patients and was treated with atropine. (page 137 under Results). Ponec et al. teach that patients with acute colonic pseudo-obstruction received 2.0 mg of neostigmine intravenously over a period of three to five minutes. This amount overlap with Applicant's amount disclosed in the specification page 7. Ponec et al. teach that acute colonic pseudo-obstruction may develop after surgery or severe illness and that colonoscopic decompression is needed to prevent ischemia and perforation of the bowel. (abstract).

Ponec et al. lack glycopyrrolate for the treatment of pseudo-obstruction and various medical conditions resulted in pseudo-obstruction, an intranasal administration, dosage ratios and frequencies.

Vavilala et al. teach that neostigmine for acute colonic pseudo-obstruction rapidly decompresses the colon in patients with acute colonic pseudo-obstruction but causes bradycardia. Vavilala et al. teach that the bradycardia is a well-recognized and important complication of neostigmine therapy. Vavilala et al. teach that the use of neostigmine is always accompanied by administration of an antimuscarinic anticholinergic agent such as atropine or glycopyrrolate to reverse this effect. (abstract).

Casadio teaches pharmaceutical composition comprising neostigmine and glycopyrronium bromide (glycopyrrolate) with a nasal carrier are suitable to be administered as intranasal formulations. (claims 1-7, particularly claims 2 and 7).

It would have been obvious to one ordinary skill in the art at time the invention was made to combine neostigmine and glycopyrrolate in bowel care or to combine to treat pseudo-obstruction in a patient because neostigmine is useful for the treatment of pseudo-obstruction by rapidly decompressing the colon and because glycopyrrolate is useful for preventing the development of adverse effect of neostigmine such as bradycardia. One would have been motivated to combine neostigmine and glycopyrrolate in a single component in order to achieve rapid decompression of colon in patients suffering from pseudo-obstruction without the complications of bradycardia, well recognized and important adverse effect of neostigmine. One would have been

motivated to make such a modification in order to prevent well-recognized and important complication well-recognized in neostigmine therapy. Moreover, it is well known by Vavilala et al. that neostigmine is always accompanied by the administration of atropine or glycopyrrolate to reverse the adverse effect result from neostigmine. With regard to the claims intranasal administration, such is obvious in view of Casadio who teach that the combination of neostigmine and glycopyrrolate are suitable for intranasal formulation. The amounts and the ratios of active agent (glycopyrrolate) to be used, the pharmaceutical forms, e.g., tablets, etc; route of administration (intranasal) and cause of resulted condition are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. One of ordinary skill in the art would optimize the dosage of glycopyrrolate taught by Vavilala in the obvious combination in order to customize the dosage needed based on the patients physical and medical profile. Furthermore, there is an expectation of successfully treating pseudo-obstruction in a patient regardless of the cause because the neostigmine comprising therapy is effective for treating such condition as taught by Ponec et al.

Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Response to Arguments

Applicants' arguments filed September 15, 2008 have been fully considered but they are not persuasive. Applicants argue that neither Ponce et al. or Vavilala et al. disclose, suggest or render obvious "a method of bowel care comprising chronically adminsitering intra-nasally a therapeutically effective amount of a drug combination comprising neostigmine and glycopyrrolate to a subject having chronic intestinal pseudo-obstruction to relieve chronic constipation, wherein the chronic intestinal pseudo-obstruction is a result of spinal cord injury and the ratio of neostigmine to glycopyrrolate is 2.5:1 to 10:1 by weight". This is not found to be persuasive because the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Casadio teaches that neostigmine and glycopyrrolate in a composition is useful and suitable to be formulated in intranasal formulations. Further, Vavilala et al. teach that neostigmine is always accompanied by administration of glycopyrrolate to reverse the adverse effect of neostigmine in colonic pseudo-obstruction therapy. Therefore one would have been motivated to combine neostigmine and glycopyrrolate in a single nasal composition for the treatment of colonic pseudo-obstruction as an alternative route. There is a reasonable expectation of successfully treating colonic pseudo-obstruction with intranasal formulation comprising neostigmine and glycopyrrolate because neostigmine

in combination with glycopyrrolate results safe and effective treatment of colonic pseudo-obstruction treatment and because these two agents are known to be formulated in an intranasal formulation in view of Casadio. Applicants argue that there is a continuous monitoring use in the operating room in the methods taught by Ponec et al. and Vavilala et al. and therefore, one of skill in the art would not predict that the disclosed therapy would be used in a chronic basis in a non-clinical setting. This is not found to be persuasive because any medical treatment provided by a medical profession is generally followed by continue monitoring by the profession. It is within the knowledge of the skilled artisan to determine and provide continue monitoring including a chronic basis when it is necessary. Further, the etiologies between acute (taught by Ponce et al.) and chronic pseudo obstruction in instant claims overlap because the subject disclosed by Ponce et al. suffering from acute pseudo obstruction was also resulted from the spinal cord injury. (left-hand side page 139). Therefore, it would prompt the skilled worker to employ the combination in colonic pseudo-obstruction in general including chronic. KSR Int'l v.Teleflex Inc., 82 USPQ2d 1385, 1395 (2007). Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER M KIM/

Primary Examiner, Art Unit 1617

Jmk
November 18, 2008